There is no PF for TCDD currently available in the Integrated Risk Information Service database (*3*). However, the PF originally derived from the aforementioned study was 156,000 mg/kg/day and may be modified downward to approximately 100,000 mg/kg/day, based on reinterpretation of histopathologic data. Applying van Birgelen's TEF to these values would suggest a PF for the carcinogenic action of HCB (under the linearized multistage assumptions) to be approximately 10–16 mg/kg/day, or about an order of magnitude more potent than is suggested by the *in vivo* data. It is possible that the difference lies in pharmacokinetic or pharmacodynamic factors that exist in the whole animal, which cannot be captured in cellular assays.

As van Birgelen points out (*1*), the World Health Organization indicates a preference for long-term *in vivo* studies over *in vitro* measures when setting a TEF (*5*). The HCB example illustrates the extreme caution that should be exercised when applying a TEF based solely on *in vitro* information, particularly when major public health claims are being made.

Bradley W. Schwab
Ogden Environmental and Energy Services Company
Westford, Massachusetts

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Response: Hexachlorobenzene

I appreciate Schwab's comments regarding caution in the use of a toxic equivalency factor (TEF) for hexachlorobenzene (HCB) based on results of *in vitro* studies. The dioxinlike effects of HCB include cytochrome P4501A induction and binding to the aryl hydrocarbon (Ah) receptor. In addition, HCB has been shown to bioaccumulate. These three factors are a prerequisite to include a compound in the TEF concept, which compares the potency of a dioxinlike compound to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). TEFs are consensus values based on available data on relative potency values for specific compounds (*1*). TEF values are used to estimate the total dioxin activity in environmental and human samples by multiplying the TEF value by the concentration of each compound, leading to a certain amount of toxic equivalents (TEQs) for each compound. The summation of all TEQs in a certain mixture expresses the total dioxin activity of this mixture. Based on the binding affinity of HCB to the Ah receptor, *in vitro* cytochrome P4501A induction, and porphyrin accumulation, a relative potency of 0.0001 for HCB was estimated (*2*). Using this relative potency value suggested that HCB could lead to a considerable contribution to the dioxin activity of human milk in some countries. I did not estimate the slope factor for HCB that is used in carcinogenicity assessment. The slope factor is the result of the application of a low-dose extrapolation procedure and is presented as the risk per milligram per kilogram of body weight per day (mg/kg/day) (*3*).

Schwab's comments included the comparison of these slope factors (although potency factors are mentioned) for HCB (1.6 per mg/kg/day) and TCDD (100,000 or 156,000 per mg/kg/day). The slope factors for TCDD are not available in the Integrated Risk Information Service database (*3*), as Schwab mentioned. He points out correctly that the ratio between these two slope factors is different from the suggested relative potency value for HCB. He assumes by using this approach that TEFs would predict the carcinogenic potential of dioxinlike compounds. However, no studies have been performed to verify this approach. Studies are currently under way to determine whether relative potency values based on biochemical effects are predictive for carcinogenesis in female Sprague Dawley rats for various dioxinlike compounds (*4*).

Angélique P.J.M. van Birgelen
NIEHS
Research Triangle Park, North Carolina

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